An Insight about Diabetic Nephropathy Diagnosis and Management

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Abstract

Background: Diabetic nephropathy is a progressive kidney disease caused by angiopathy of capillaries in the kidney glomeruli. It is characterized by nephrotic syndrome and diffuse glomerulosclerosis. It is due to longstanding diabetes mellitus.Diabetic Nephropathy is the leading cause of chronic kidney disease in patients starting renal replacement therapy and is associated with increased cardiovascular mortality. Clinically, DN has been characterized by a progressive increase in albumin excretion ratio (AER), a decline in GFR, and an increase in BP. With the increasing use of RAAS blocker in diabetic patients, DN with normoalbuminuria or low microalbuminuria but declining eGFR has been described. Renal involvement is diagnosed to be secondary to diabetes in the setting of long-standing diabetes with diabetic neuropathy or diabetic retinopathy particularly in type I diabetics, where there is a good correlation. Renal manifestations in diabetes are classified into five stages including glomerular hyperfiltration, normoalbuminuria, microalbuminuria, macroalbuminuria, and finally ESRD. The goals of treatment are to slow the progression of kidney damage and control related complications. In normo- or microalbuminuric subjects, the aim of treatment is to intervene at arterial hypertension, hyperglycemia, smoking habit and probably dyslipidemia. Even in the absence of clear data showing that the management of these risk factors individually is beneficial to DN, they are also risk factors for cardiovascular disease and should be aggressively treated.

Keywords: Diabetic Nephropathy

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Introduction

Diabetic nephropathy is a progressive kidney disease caused by angiopathy of capillaries in the kidney glomeruli. It is characterized by nephrotic syndrome and diffuse glomerulosclerosis. It is due to longstanding diabetes mellitus.Diabetic Nephropathy is the leading cause of chronic kidney

disease in patients starting renal replacement therapy and is associated with increased cardiovascular mortality (1).

Diabetic nephropathy (DN) is defined in both type 1 and type 2 diabetes as the presence of persisting severely elevated albuminuria of more than 300 mg/24 h or an albumin creatinine ratio > 300 mg/g creatinine, confirmed in at least two out of three samples, with concurrent presence of diabetic retinopathy and absence of signs of other forms of renal disease. As such, it is a clinical diagnosis, requiring little more than basic clinical and laboratory evaluations. Normal value for albuminuria has been defined as <30 mg/g (or 30 mg/24 h), and abnormal values above 30, but albuminuria is a continuous measurement and increasing values within the normal and abnormal range are associated with elevated risk for renal and cardiovascular disease (2).

Prevalence of diabetic nephropathy: Globally, an estimated 536.6 million people, or 10.5% of the population, have diabetes according to the International Diabetes Federation (IDF) Diabetes Atlas update of 2021. It is estimated that by the year 2045, 783.2 million people, will have diabetes (3).

In an analysis of data from the Center for Disease Control and Prevention Diabetes Surveillance System, reported in 2022 a prevalence of diagnosed diabetes of approximately 11.3 percent of adults (37.3 million people; 28.7 million with diagnosed diabetes, an estimated 8.5 million undiagnosed, and 95 percent of whom have type 2 diabetes) (4). CKD is estimated to affect 50% patients with T2DM globally, and its presence and severity markedly influences disease prognosis. CKD is more common in certain patient populations, including the elderly, those with youth-onset diabetes mellitus, those who are obese, certain ethnic groups, and disadvantaged populations. (5) The prevalence of DN is still rising dramatically, with concomitant increases in associated mortality and cardiovascular complications (6). AS GOES OBESITY, SO GOES diabetes… In the United States, progressive increases in rates of obesity and diabetes have occurred in parallel (7). In most states, prevalence's of obesity and diabetes among adults now exceed 30% and 10%, respectively. Both rates have more than doubled in just 2 decades. But this is not just an American phenomenon. There has been a worldwide explosion of diabetes (8).

Pathogenesis of Diabetic Nephropathy DN can be characterized by several morphological changes that involve all sections of the kidney, which affect the function of the organ. The series of alterations include the thickening of the basement membrane and the formation of nodular glomerulosclerosis within the glomeruli. The transformation in nature of the glomerular basement membrane (GBM) from its normal collagen chains, a1 (IV) and a2 (IV) to more restricted collagen chains, a3 (IV) and a4 (IV) results in the accumulation of type IV collagen in the lamina of the GBM (9). As the disease progresses, more layers of the GBM are filled with these extracellular matrix components, which further expand the GBM by approximately twice the normal size. This affects the compositional quality and function of the GBM leading to proteinuria or macromolecular leakiness. Besides that, the build-up of extracellular mesangial matrix components and to some extent, mesangial cell proliferation causes mesangial expansion within the glomerulus. This along with collagen deposition subsequently leads to glomerulosclerosis, which is the formation of eosinophilic nodules known as Kimmelsteil-Wilson nodules and finally tubulointerstitial fibrosis (10). Involvement of pro-inflammatory cytokines in diabetic nephropathy

Studies have shown that tumor necrosis factor (TNF)-α is increased in serum and urine of patients

affected by DN as compared to control (diabetic and non-diabetic patients), which are associated with the progression of renal injury. Moreover, the association between TNF-aIL-6, IL-1 and pathogenesis of DN, which are known to participate in the impairment of the inter-glomerular hemodynamic had been reported (9). Risk factors The two main risk factors for DN are hyperglycemia and arterial hypertension. However, DN develops in only about 40% of patients, even in the presence of hyperglycemia and elevated BP for long periods of time. This observation raised the concept that DN will develop only in a susceptible subset of patients. Furthermore, family studies have confirmed a genetic contribution for the development of DN in both type I and type II DM (11).

Increased albuminuria ** Increase excretion of albumin in the urine is a major risk factor for the development and progression of kidney disease in people living with diabetes. It is characterized by increased excretion of albumin/g creatinine in the urine referred to as microalbuminuria (30–300 mg/g) or macroalbuminuria (> 300 mg/g) (11).**

Hyperglycemia
Hyperglycemia is considered as one of the most prominent and independent risk factors of DN. It increases the worsening of renal function by altering the antioxidant system which leads to the increased Formation of advanced glycation end products. Polyol pathway activation is also postulated in the pathogenesis of DKD. Variability in glycated hemoglobin (HbA1c) is associated with the development and progression of nephropathy in both type 1 DM patients and T2DMM patients. A similar finding was reported by the Renal Insufficiency and Cardiovascular Events (RIACE) an Italian multicenter study.26Evidencefrom randomized controlled trials found beneficial effects of intensive glucose control in the delayed onset as well as in preventing the progression of albuminuria in T2DMM patients (12). In the presence of micro- and macro-albuminuria the role of metabolic control is less defined, even though some studies showed a deleterious effect of high glucose levels on GFR. Moreover, it was demonstrated that pancreas transplantation reversed renal damage in type I DM patients with mild to advanced DN lesions (12).
Arterial hypertension Hypertension is a pivotal risk factor for diabetic nephropathy. Hypertension is significantly associated with the development of diabetic nephropathy as confirmed by a recent meta-analysis. Hypertensive patients are at higher risk of developing diabetic nephropathy as compared to non-hypertensive patients with an odds ratio of 1.67 (95% CI: 13.1–2.14) (12). This was further confirmed by a population-based prospective study from china which states that hypertension control can reduce the incidence of end stage kidney failure by 23% (11).
Dyslipidaemia
Dyslipidemia plays an important role in the development and progression of DKD. The impact of dyslipidemia on renal function impairment was described by the lipid nephrotoxicity hypothesi.In people with diabetes, dyslipidemia is characterized by a decrease in high density lipoprotein, and an increase in triglycerides, low-density lipoprotein, and very low density lipoprotein (13).

Dyslipidemia has a role in the development of DN by causing apoptosis of podocytes, macrophage infiltration, and excessive production of extracellular matrix. Hyperglycemia and insulin resistance could aggravate dyslipidemia in DN patients (11).

Obesity

Evidence suggests a strong association between obesity and DN. The mechanism by which obesity leads to DN is not clear but it is presumed that obesity leads to glomerular injury, glomerular hypertrophy, and proteinuria (11).

Smoking

Smoking is considered as an independent risk factor in the development and progression of diabetic nephropathy. The pathogenic role of smoking in the development of diabetic nephropathy is multifactorial including oxidative stress, hyperlipidemia, deposition of advanced end glycation products, and glomerulosclerosis (14).

Evidence form a finish diabetic nephropathy study on 3613 type 1 DM patients found a higher risk of albuminuria and end stage renal disease in smokers as compared to non-smokers. The risk of diabetic nephropathy was found to be increased with the dose of smoking. This was also confirmed by a recent meta-analysis based on the pooling of nine cohort studies which concludes that smoker T2DM patients are at an increased risk of developing diabetic nephropathy (15).

Dietary factors

Increased dietary protein intake seems to be associated with the presence of higher UAE values, at least in patients with type I DM. In patients with type II DM, this association has not been documented. The source of proteins in the diet also seems to be related to the presence of DN. A higher intake of fish protein is related to a lower risk of microalbuminuria in type I DM patients. The mechanisms involved in these findings are unknown but probably related to hemodynamic factors (16).

Regarding the dietary lipid content, an association has been observed between the higher intake of saturated fat and the presence of microalbuminuria in patients with type I DM. In patients with type II DM, it was observed that the presence of microalbuminuria was associated with the lower content of polyunsaturated fatty acids, especially those of vegetal origin (16).

Clinical Diagnosis

Clinically, DN has been characterized by a progressive increase in albumin excretion ratio (AER), a decline in GFR, and an increase in BP. With the increasing use of RAAS blocker in diabetic patients, DN with normoalbuminuria or low microalbuminuria but declining eGFR has been described (2).

Renal involvement is diagnosed to be secondary to diabetes in the setting of long-standing diabetes with diabetic neuropathy or diabetic retinopathy particularly in type I diabetics, where there is a good correlation. Renal manifestations in diabetes are classified into five stages including glomerular hyperfiltration, normoalbuminuria, microalbuminuria, macroalbuminuria, and finally ESRD (17).

The first laboratory abnormality is a positive microalbuminuria test. Most often, the diagnosis is suspected when a routine urinalysis of a person with diabetes shows too much protein in the urine (proteinuria). The urinalysis may also show glucose in the urine, especially if blood glucose is

poorly controlled. Serum creatinine and Blood urea nitrogen (BUN) may increase as kidney damage progresses (18).

A kidney biopsy confirms the diagnosis, although it is not always necessary if the case is straightforward, with a documented progression of proteinuria over time and presence of diabetic retinopathy on examination of the retina of the eyes (19).
But recently, as there is a close relationship between the pathology and prognosis of T2DM related CKD, renal biopsy and pathological classification to DKD are of great importance in early diagnosis and personalized treatment, and to evaluate the prognosis of disease. The renal biopsy was positively advised to carry out and avoid the misdiagnosis and improved the treatment accuracy of diabetes related to kidney damage (20).

In T1DM, a clinical diagnosis of DKD can be made when there is persistent moderate (A2) or severe (A3) albuminuria or a persistent reduction in eGFR to <60 mL/min/1.73 m2, occurring at least 5 years after onset of diabetes. In over 95% of cases, diabetic retinopathy will also be present, and there should be no clinical suggestions of alternative kidney disease. Albuminuria is not required to make a diagnosis of DKD in the setting of a persistently reduced eGFR, but this clinical scenario should prompt consideration of other forms of non-albuminuric kidney disease, as should albuminuria in the absence of retinopathy (2).

In T2DMM, the clinical diagnosis can be more challenging due to the increased heterogeneity of clinical presentation, although the same principles of persistent albuminuria or persistently reduced eGFR apply. Again, albuminuria does not have to be present to make a diagnosis of DKD providing eGFR is persistently <60 mL/min/1.73 m2. Longer duration of diabetes and presence of retinopathy are important pointers towards the diagnosis when they are present, but neither a short duration of diabetes nor absence of retinopathy are useful to rule out DKD in T2DMM. It is therefore important to evaluate for features that may indicate alternative forms of kidney disease and proceed to renal biopsy when there is diagnostic uncertainty.

If a reduction in eGFR or an increase in albuminuria is detected, this should be confirmed on repeat testing over 3 to 6 months; a minimum of two elevated ACR levels more than 3 months apart are required before an individual is considered to have increased albuminuria. This is to differentiate from transient changes as well as to account for the intra-individual variation that is seen in ACR. Similarly, two eGFR values below 60 mL/min/1.73 m2 at least 90 days apart are required to make a diagnosis of CKD (21).

DN screening must be performed when DM is diagnosed in patients with type II DM, since these individuals may have had a silent form of DM for some time already. For patients with type I DM, it is recommended that screening be performed beginning in the fifth year after DM diagnosis or earlier if the DM is chronically poorly compensated, or if the patient is an adolescent. In all cases, if albuminuria is normal, screening must be repeated annually (21).

Although the measurement of albuminuria is essential to diagnose DN, there are some patients who present decreased GFR when urine albumin excretion (UAE) values are normal. Based on this, the classification of the National Kidney Foundation can also be used to stage chronic kidney disease in these patients (21).

Patients with micro- or macro-albuminuria, after the confirmation of diagnosis (2 measurements), should undergo a complete evaluation concerning differential diagnosis and assessment of renal function (2).

Absent retinopathy, short duration of DM and faster decline in GFR and/or albuminuria increment are indications to suspect nondiabetic renal disease. If after a non-invasive evaluation the diagnosis is still unclear, a kidney biopsy should be discussed. In type II DM, the prevalence of nondiabetic renal disease could vary from 12 to 38%. All the kidney biopsy data are derived from retrospective studies. The differences in the prevalence of non-diabetic lesion observed in the studies probably reflect different criteria used to indicate renal biopsies (22).

Treatment:
The goals of treatment are to slow the progression of kidney damage and control related complications. In normo- or microalbuminuric subjects, the aim of treatment is to intervene at arterial hypertension, hyperglycemia, smoking habit and probably dyslipidemia. Even in the absence of clear data showing that the management of these risk factors individually is beneficial to DN, they are also risk factors for cardiovascular disease and should be aggressively treated (20). There are two overarching aims in the management of DN: preserving renal function to reduce the risk of ESKD; and reducing the risks of cardiovascular events and mortality. In addition, people with DKD are also more likely to experience retinopathy, neuropathy and foot ulcers so increased vigilance for these complications is important. Treatment guidelines have been developed by several international and national organizations and are summarized in Table 1

Table (1): Goals of treatment in DN

Kdigo (2012) Easd (2019) Ada (2020) Nice (2014)

	KDIGO (2012)	EASD (2019),	ADA (2020)	NICE (2014)
Dietary sodium	<2 g/day (or < 5 g/day salt)	-	<2300 mg/day	-
Physical activity	>150 min/week moderate intensity	>150 min/week aerobic and resistance activity	>150 min/week aerobic activity	>150 min/week moderate intensity, aerobic activity
Weight loss	Achieve healthy weight (BMI 20-25 kg/m^2)	Weight stabilization if BMI ≥ 25 kg/m^2	>5% weight loss if BMI ≥ 25 kg/m^2	Initial target 5-10% weight loss if BMI ≥ 25 kg/m^2
Smoking cessation	Recommended	Obligatory	Advise against tobacco and e-cigarettes	Recommended

Blood pressure	<130/80 if albuminuria present	SBP < 130 mmHg but not <120 DBP < 80 mmHg but not <70 If >65 years: SBP 139-130 mmHg	<130/80 mmHg if 10-year CV risk ≥15% <140/90 if lower risk	<130/80 mm
HBA1C	<7% for most patients Higher target if risk of hypoglycaemia, severe comorbidities, or limited life expectancy	<7% for most patients <6.5% for early stages of diabetes and younger patients <8% in elderly or those with severe multimorbidity	<7% for most patients <6.5% if low risk of hypoglycaemia <8% if high risk of hypoglycaemia of multimorbidity	<7.0% if risk of hypoglycaemia <6.5% if low risk of hypoglycaemia Relax target if: High risk of hypoglycaemia Reduced life expectancy Severe multimorbidity Elderly or frail

Abbreviations: ADA, American Diabetes Association; BMI, body mass index; CKD, chronic kidney disease; CV, cardiovascular; DBP, diastolic blood pressure; EASD, European Association for the Study of Diabetes; GFR, glomerular filtration rate; HBA1C, haemoglobin A1C; KDIGO, Kidney Disease Improving Global Outcomes; LDL-C, low density lipoproptein cholesterol; NICE, National Institute for Health and Care Excellence; RAASi, renin-angiotensin-aldosterone system inhibitor; SBP, systolic blood pressure.

Lipid lowering and CV risk reduction

The onset of kidney disease in people with diabetes portends a significant increase in the risk of cardiovascular mortality, and as such aggressive risk factor modification is warranted in all patients. This includes smoking cessation and lipid lowering; the importance of blood pressure lowering is discussed later. It is a component of combination therapy that has been shown to improve outcomes in the Steno-2 trial (23).

Renin-Angiotensin System (RAS) blockade:

The main treatment, once proteinuria is established, is Angiotensin converting enzyme (ACE) inhibitor drugs, which usually reduces proteinuria levels and slows the progression of diabetic nephropathy. Several effects of the Angiotensin converting enzyme inhibitors (ACEIs) that may contribute to renal protection have been related to the association of rise in Kinins which is also

responsible for some of the side effects associated with ACEIs therapy such as dry cough. The renal protection effect is related to the antihypertensive effects in normal and hypertensive patients, renal vasodilatation resulting in increased renal blood flow and dilatation of the efferent arterioles (24).

RAS blockade with ACE inhibitors or ARB confers an additional benefit on renal function. This renoprotective effect is independent of BP reduction. These drugs decrease UAE and the rate of progression from microalbuminuria to more advanced stages of DN (24).

The large trial (ONTARGET) in diabetic and nondiabetic subjects showed that the association of the two classes of drugs had a major effect on decreasing proteinuria but not on GFR decline or mortality (25). In fact, a worse effect on GFR and mortality was observed. Analysing the subgroups, the increased mortality came from the less sick subjects. Among diabetic subjects no increased mortality was observed, but also no benefit from the dual blockage was observed (25).

Another step that has been proposed to be blocked is the aldosterone action. Adding the aldosterone antagonist (spironolactone) to ARBs or ACE inhibitor is also more effective in reducing UAE and BP in type II diabetic patients than each drug alone (26).

Finerenone is a new nonsteroidal Mineralocorticoid Receptor Antagonist (MRA) with increased receptor selectivity compared to spironolactone and greater receptor affinity than eplerenone in vitro, along with a less frequent occurrence of hyperkalemia than spironolactone (27).

** A trial that recruited patients with type II DM and urine albumin to creatinine ratio (UACR) above 30 mg/g, finerenone added to ACEi or ARB produced a dose dependent decrease in UACR without inducing hyperkalemia at day 90 (28). **

Hyperglycemia treatment pecularities:

The treatment of DM is not the aim of the present review, but a few special remarks could be made regarding the treatment of hyperglycemia in a patient with renal disease. Metformin is the standard therapy for patients with type II DM and will only be briefly discussed here. Metformin is contraindicated when serum creatinine is above 1.5 mg/dl in men and 1.4 mg/dl in women due to the increased risk of lactic acidosis. However, these values are being questioned. In these creatinine ranges, some subjects will be using metformin on chronic renal disease stages II and III (2).

A current United Kingdom (UK) guideline on the treatment of T2DM allows metformin use up to a GFR of 30 mL/min/1.73 m2, with dose reduction advised at 45 mL/min/1.73 m2. In the USA, metformin is contraindicated for men with serum creatinine ≥ 1.5 mg/dL and for women with serum creatinine ≥ 1.4 mg/dL (2).

New evidence from the literature suggests that patients with mild-to-moderate DKD face more benefits than risks while using metformin. In fact, the REduction of Atherothrombosis for Continued Health (REACH) Registry 2004 showed decreased mortality associated with metformin use, even in patients with moderate kidney disease (29)
** Nonetheless, the use of metformin is still avoided in patients with CKD stages 3–5 with other associated risk factors for lactic acidosis. However, studies based on experimental and cell culture models have shown a potential renal protective effect for metformin. In these studies, metformin

prevented glucose-induced oxidative stress in podocytes by inhibiting NAD(P)H oxidase; decreasing 8-hydroxydeoxyguanosine (8-OHdG), a supposed marker of total systemic oxidative stress and DNA damage in vivo; and also improving the free-radical defense system (30).**

NOVEL THERAPEUTIC MODALITIES:

Pleotropic renoprotective effects of anti-diabetic drugs beyond glycemic control:

Certain hypoglycemic agents have been shown to confer independent renoprotective effects beyond their hypoglycemic action. For instance, peroxisome proliferator activator receptor-gamma (PPAR-γ) agonists, also known as thiazolidinediones (TZD), have direct renoprotective effects in experimental models (31).

However, reports from clinical studies have been varied, with some achieving encouraging results by lowering proteinuria (31).

Rosiglitazone has been shown to decrease Urinary Albumin Excretion (UAE) in type II diabetic patients as compared to glyburide, suggesting a beneficial effect in the prevention of renal complications of type II DM. This antiproteinuric effect occurs also in nondiabetic disease (32).

Glucagon-like peptide I (GLP- I) , an incretin which promotes insulin and suppresses glucagon release, is produced by the gut when food is ingested and it is degraded by dipeptidyl peptidase-4 (DPP-4) (32).

A novel group of hypoglycemic agents in the form of DPP-4 inhibitors have emerged in the treatment paradigm of DM, and experimental models have indicated possible renoprotective benefits. Currently, data has only been obtained from a few clinical trials; however, in small, uncontrolled studies, 6 months Sitagliptin or 12 weeks of alogliptin lowered albuminuria in patients with type II DM (33).

** There are five available DPP-4 inhibitors, also known as"gliptins" (sitagliptin, vildagliptin, saxagliptin, linagliptin and alogliptin), and despite their common mechanism of action, these agents have structural heterogeneity that translates into different pharmacological properties, different metabolism and excretion pathways (34).**

Sitagliptin is mostly eliminated unchanged in the urine and can be used with appropriate dose reduction in all chronic kidney stages. The usual dose of 100 mg once per day should be adjusted to 50 mg/day for patients with moderate renal impairment. In severe renal impairment (creatinine clearance < 30 mL/min) or end stage renal disease (ESRD) requiring dialysis, the dose is further reduced to 25 mg once daily (33).

Vildagliptin is metabolized, mostly in the kidneys, into inactive metabolites. Its main route of elimination is hydrolysis by multiple tissues or organs and approximately 25% of the drug is excreted unchanged by the kidneys. In type II diabetes patients and patients with moderate-to-severe CKD, dose reductions for vildagliptin are required, which means a reduction by half (to 50 mg/day) for both moderate and severe CKD (35).

** Saxagliptin is metabolized, mainly in the liver, into an active metabolite that is eliminated in the urine. The normal dose (5 mg once daily) should be reduced to 2.5 mg once daily in patients with

moderate or severe renal impairment and excluded for patients with ESRD requiring hemodialysis (36).**

Meanwhile, linagliptin is the only DPP-4 inhibitor that is eliminated nearly entirely via the bile, thus making this agent a possible treatment choice for patients with normal kidney function as well as for patients in all stages of CKD, and even stage 5 (GFR <15 mL/min/ 1.73 m2), without dose adjustments (37).

** Alogliptin is primarily excreted unchanged in the urine and the usual dose is 25 mg once per day. However, for individuals with a decreased filtration rate, the dosage should be adjusted. Therefore, for patients with a creatinine clearance rate between 30 and 60 mL/min, the dose is 12.5 mg per day, whereas for those with greater loss of renal function or hemodialysis, the recommended dose is only 6.25 mg/day (38).**

Exenatide is a GLP-1 analog. Subcutaneous applications (beginning at 5 μg bid for 30 days and then 10 μg bid) should be performed up to one hour before meals twice a day. It is a drug that reduces weight, which may be an advantage in managing the diabetic patient. The major side effects are nausea and vomiting, what occasionally an individual cannot tolerate using it. It is metabolized and excreted by the kidneys. It presents a low risk of hypoglycemia and can be used in stage 3, and it is not recommended in stages 4 and 5 due to the increased risk of side effects (39).
Lixisenatide is eliminated through glomerular filtration, followed by tubular reabsorption and subsequent metabolic degradation, resulting in smaller peptides and amino acids that are introduced into protein metabolism. However, data from patients with kidney disease are limited (40).
** In persons without diabetes, mild to moderate renal impairment did not appear to affect the drug's pharmacokinetics or safety, but drug exposure was increased in persons with severe renal impairment, suggesting the need for dose adjustment in this population (41).**

** Finally, liraglutide is metabolized in a manner similar to that for large proteins and its elimination is not related to a specific organ. Currently, its prescription in patients beyond mildstage renal disease is limited and there are no recommendations that support its use in the moderate and severe stages (41).**

Vitamin D receptor activators:

Vitamin D receptor (VDR) activators demonstrated anti-inflammatory and antiproteinuric effects in animal models of DN (42). Findings from the phase III VITAL (Selective Vitamin D Receptor Activation with Paricalcitol for Reduction of Albuminuria in Patients with Type II Diabetes) trial indicate that adjuvant paricalcitol at 2 μ g/day lowers residual albuminuria in DN (43).

** However, 42% of patients needed a reduced dose of paricalcitol due to poor tolerance, not to mention the additional drawback of the high cost of treatment. Therefore, concrete evidence demonstrating the successful use of VDR activators to retard the progression of DN is still awaited (44).**
Sodium-glucose cotransporter 2 inhibition:

Apart from their ability to enhance urinary glucose excretion and aid glycemic control, SGLT-2 inhibitors appear to also promote blood pressure and body weight optimization (45).

In the EMPA-REG study (46) that has recruited over 7,000 type 2 diabetics at high cardiovascular risk, empagliflozin when added to standard care reduced the rates of death from cardiovascular causes (3.7%, vs. 5.9% in the placebo group; 38% relative risk reduction [RRR]), hospitalization for heart failure (2.7% and 4.1%, respectively; 35% RRR), and death from any cause (5.7% and 8.3%, respectively; 32% RRR). Unpublished data (presented at the American Society of Nephrology Kidney Week 2015 in San Diego) on renal outcomes are also promising, with significant reductions in new onset or worsening of nephropathy and the composite renal endpoints of doubling of serum creatinine, initiation of renal replacement therapy or death from renal cause.

This therapeutic class has been approved for the treatment of patients with T2DM with an eGFR of ≥ 45 mL/min/1.73 m2. To date, however, just canagliflozin has been evaluated, showing safety and efficacy in a subset of patients with stage 3 CKD (46).

Selective C-C chemokine receptor type 2 antagonism:

Monocyte chemoattractant protein- I (MCP- I), also called C-C chemokine ligand 2 (CCL2), one of the ligands for C-C chemokine receptor type 2 (CCR2), has been implicated not only in insulin resistance but also in progressive renal injury, and has been suggested to be a potential marker of renal disease. In DN, MCP- I overexpression plays an indispensable role in promoting monocyte and macrophage migration and activation (47).

CCX140-B is a small molecule CCR2 antagonist that inhibits CCR2 and blocks MCP-I-dependent monocyte activation and chemotaxis. Data from preclinical studies suggested that oral CCX140-B improved glycaemia and albuminuria in a mouse model of diabetes (48).

The first evidence that CCR2 inhibition lowers albuminuria in DN came from a European study (49).

Dietary intervention:

There are several modalities for a dietary intervention in DN, whether changing protein content or through the manipulation of lipid content. However, few have their efficacy shown based on long term randomized clinical trials (2).

In patients with type I DM, in different stages of renal disease, protein restriction in the diet has shown that it can reduce the decline of renal function and albuminuria. According to a meta-analysis of studies performed with type I DM patients and clinical nephropathy, dietary protein restriction retards DN progression (2).

American Diabetes Association (2019) recommended for people with no dialysis-dependent diabetic kidney disease, dietary protein intake should be approximately 0.8 g/kg body weight per day (the recommended daily allowance). Compared with higher levels of dietary protein intake, this level slowed GFR decline with evidence of a greater effect over time. Higher levels of dietary protein intake (> 20% of daily calories from protein or > 1.3 g/kg/day) have been associated with increased albuminuria, more rapid kidney function loss, and CVD mortality and therefore should

be avoided. Reducing the amount of dietary protein below the recommended daily allowance of 0.8 g/kg/day is not recommended because it does not alter glycemic measures, cardiovascular risk measures, or the course of GFR decline.

Dyslipidemia:
The desired target of LDL is < 100 mg/dl for patients with DM in general, and < 70 mg/dl when cardiovascular disease is present. No data based on a large clinical trial is available showing that the treatment of dyslipidemia is able to prevent the development or progression of DN (50).

In the Heart Protection Study (HPS), simvastatin, 40 mg, reduced vascular event rates and GFR decline in patients with DM by 25%, independent of baseline cholesterol levels. Furthermore, the results of the Collaborative Atorvastatin Diabetes Study (CARDS) demonstrated a marked reduction in cardiovascular events in DM patients, and at least one additional risk factor for coronary disease, suggesting that all DM patients should use statins. The later publication of CARDS showed a modest beneficial effect of atorvastatin on eGFR, particularly in those with albuminuria. However, atorvastatin did not influence albuminuria incidence (50).

In the Greek atorvastatin and coronary heart disease evaluation (GREACE) 40 patients given atorvastatin had a significant reduction in urinary albumin excretion; however, separate analysis for type II diabetes was not included in the study (49).. Such findings have been echoed by the PLANET I study, in which treatment with atorvastatin 80 mg lowered UPCR substantially more than rosuvastatin 10 mg (-15·6%, 95% CI -28·3 to -0·5; p = 0·043) or rosuvastatin 40 mg (-18·2%, -30·2 to -4·2; p = 0·013). It must be cautioned that such doses of atorvastatin are unusually high for the average CKD patient (49).

Multifactorial intervention:

Probably, the best approach to a subject with DN is a multifactorial intervention. However, only one study, with a small number of patients (n = 160) addressed this aspect (51).

** In this study the targets were: BP levels < 130/80 mmHg, fasting serum cholesterol < 175 mg/dl, fasting serum triglycerides < 150 mg/dl, and HbA1c < 6.5%. The intervention consisted of a stepwise implementation of lifestyle changes and pharmacological therapy including low-fat diet, three to five times a week light-to-moderate exercise program, smoking-cessation course, and prescription of ACE inhibitors or ARB and aspirin. The multiple intervention group had a 61% reduction in the risk of macroalbuminuria, and a 58% and 63% reduction in the risk of retinopathy and autonomic neuropathy, respectively. Most importantly, a 55% reduction in the risk for the development of a composite endpoint consisting of death from cardiovascular causes, non-fatal myocardial infarction, revascularization procedures, non-fatal stroke and amputation was also associated with the multifactorial intervention. It is important to point out that even among highly motivated subjects only a small number reached the proposed goals. Less than 20% in the intensive arm reached the HbA1c goal and less than 50% the systolic BP goal (51)**

**Despite improved understanding of the pathophysiology of DN over the last 2 decades, an effective and specific treatment for this inexorable condition remains limited as the incidence of type II DM is predicted to continue an exponential upward trajectory, particularly in the developing world

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